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Taar1 as a Therapeutic Target

We previously applied gene mapping, biochemical and genetic tools, and behavioral analysis to identify and validate a single nucleotide polymorphism in trace amine-associated receptor 1 (Taar1) accounting for 60% of the genetic variance in voluntary methamphetamine (MA) intake in mouse lines selectively bred for high vs. low intake. TAAR1-specific agonists have therapeutic potential for drug-use disorders via their ability to reduce drug-induced increases in dopamine signaling and through additional effects that shift the reward:aversion balance away from drug-induced reward. We examined the impact of the potent TAAR1-specific agonist, RO5256390 (RO), on the rewarding effects of morphine and repeated these studies with MA, a TAAR1 agonist with independent dopamine-elevating effects increasingly co-used with opioids. Both RO and MA induced conditioned aversion that was blocked by morphine. RO blocked morphine-induced conditioned reward in the non-drug state but not in the drug-present state, supporting therapeutic potential during abstinence. RO and MA had hypothermic effects that were synergistically accentuated by morphine, and this accentuation was also found for fentanyl and MA. Combined locomotor depressant effects of RO and MOR were like those of RO alone. Locomotor depressant effects of morphine were reversed and similar to the locomotor stimulant effects of MA alone. These data provide a unique picture of the combined effects of TAAR1 agonists and opioids. During therapeutic development, it will be important to broadly consider behavioral and physiological effects of TAAR1 agonists with opioids and other drugs because relapse to drug-taking could occur at the time of TAAR1 agonist treatment. Supported by NIH/NIDA R01DA046081 and R01DA057420, and the Department of Veterans Affairs Senior Research Career Scientist Program IK6BX006342.

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